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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/734,300	12/11/2000	Victor Koteliansky	A058 US	6220

7590 11/26/2001

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EXAMINER
ANDRES, JANET L

ART UNIT	PAPER NUMBER
1646	8

DATE MAILED: 11/26/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/734,300	KOTELIANSKY ET AL.	
	Examiner	Art Unit	
	Janet L Andres	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *7,8 and 10-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9 and 13-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, polypeptides, with traverse and species election of arthritis in Paper No. 7 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse and is made FINAL (MPEP § 818.03(a)). Claims 1-21 are pending in this application. Claims 7, 8, and 10-12 are withdrawn from consideration as being drawn to a non-elected invention.

The Examiner notes that, since the sequences are misidentified in the specification and claims (see below), those claims drawn to specific sequences were interpreted to be drawn to SEQ ID NO: 9 as requested by Applicant's representative, John Li, by telephone on 13 November 2001.

Specification

2. The disclosure is objected to because of the following informalities: There are blank spaces and question marks on page 25. In addition, "SEQ ID NO:2" is continually referred to as an amino acid sequence. It is a polynucleotide sequence. In addition, SEQ ID NO:1, referred to as containing a human sequence on p. 13, is described as a rabbit sequence in the sequence listing. There is an amino acid sequence on p. 25 that lacks a sequence identity number; the sequence rules embrace all unbranched nucleotide sequences with ten or more bases and all unbranched, non-D amino acid sequences with four or more amino acids whether claimed or not. See MPEP §2421.02. Beginning on p. 35, a symbol is used in place of "beta" that is not the standard Greek letter β. Correction is required. The Examiner additionally notes that, contrary

to the teachings of the specification, neither amino acid sequence set forth in the application appears to be taught by Suzuki et al. or Nikawa. The instantly taught sequences appear to lack the insert taught by these references and the initial 160 amino acids of SEQ ID NO: 9 appear to be identical to the receptor taught by Lin et al., U.S. patent 6046157. However, the Examiner also notes that the first 140 residues of SEQ ID NO:9 are misnumbered.

Claim Objections

3. Applicant is advised that should claim 4 be found allowable, claim 6 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for TGF-β RII/Fc fusion proteins of SEQ ID Nos: 8 and 9, does not reasonably provide enablement for all TGF-β R fusion proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working

examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex Parte Forman,* (230 USPQ 546 (Bd Pat. App. & Int. 1986)); *In re Wands,* 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988). Claims 1-3 are broadly drawn. Claim 1 encompasses all "splice variants" of all TGF-β R proteins, including proteins not yet known in the art that could be so described. Claims 2 and 3 are limited only to splice variants of TGF-β R II, not just that disclosed by Applicant, again including those that have not yet been described. Claims 1 and 2 additionally comprise any other protein. In addition, these claims require the ability to inhibit binding of "TGF-β" to a receptor. Applicant has not, however, provided sufficient guidance for one of skill in the art to make and use the proteins as broadly claimed. Massagué (Ann. Rev. Biochem. 1998, vol. 67, pp. 753-791) teaches that TGF-β receptors have different binding properties: the type I receptor, encompassed by claim 1, can not bind TGF-βs independently of the type II receptor (p. 762). While Applicant teaches that the instant splice variant of TGF-β RII binds all three forms of TGF-β, TGF-β2 binds the normal type II receptor weakly in the absence of the auxiliary receptor betaglycan (Massagué, p. 763). Thus, one of skill in the art could not predictably use all molecules potentially within the scope of the claims to bind all forms of TGF-β and to bind them with sufficient affinity to inhibit binding to other receptors. While TGF-β binding regions are known in the art, there is no guidance in the instant specification as to what insertions or deletions would maintain sufficient binding to be useful, and what possible variants would not meet the limitations of the claims. Thus one of skill in the art would require additional guidance, such as information as to what structural features would result in inhibition of TGF-β interaction with other receptors, in order to practice the invention commensurate with the scope

of the claims. Furthermore, claims 1 and 2 encompass all fusion partners. There is no indication as to what additional molecules other than immunoglobulins could be used without affecting the ability of the molecule to bind TGF-β, and no direction as to how one of skill in the art might determine what other molecules could be used. Thus, without further direction as to what molecules might be predicted to fall within the scope of the claims, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

6. Claims 13-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. These claims are drawn to methods of decreasing TGF-β levels using residues 1-185 of SEQ ID NO:2, which is presumably intended to be the soluble TGF-β RII region of the fusion protein, and of treatment of disease by decreasing these levels. The claims require not only that the antagonist bind TGF-β, but that it do so well enough to reduce levels of TGF-β *in vivo* and that it reduce levels of whatever isoforms of TGF-β might be present in the disease state. Claims 15-21 require that this reduction be sufficient to cause a therapeutic effect. While Applicant has provided guidance to indicate that the fusion protein of the splice variant of TGF-β RII (presumably) can lower levels of TGF-β *in vitro*, Applicant has provided no guidance to indicate that this protein or a protein comprising the first 185 residues of this protein would have an effect on TGF-β levels *in vivo* or that this effect, if observed, would be of sufficient magnitude to affect the course of disease. *In vitro* evidence is not predictive of *in vivo* results. Such factors as binding affinity, as on/off rates, as protein stability, and as accessibility to the targeted ligand all affect the ability of a therapeutic agent to function *in vivo*. Thus, without further guidance, one

of skill in the art would not predict that the claimed invention could be used to usefully affect TGF-β levels *in vivo*, and, without such guidance predictive of a successful result, it would require undue experimentation for the skilled artisan to practice the invention as claimed.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-6 and 13-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is drawn to splice variants. However, there is no definition of "splice variant" in the specification. Claim 2 and, by dependency, claim 3, are drawn to "the splice variant"; since this term is not defined, one of skill would not be able to determine what proteins, including the receptor first cloned, which is a variant of that with the insert, and including variants not yet known in the art, were encompassed by the claims.

Claims 4, 6, 9, and 13-21 are drawn to proteins or methods requiring the polypeptide of SEQ ID NO:2. However, as stated above, the molecule represented by SEQ ID NO: 2 is a polynucleotide. In addition, as stated above, no sequence appears to correspond to that used by Applicant. Thus one of skill in the art would not be able to determine what proteins were encompassed by these claims.

Claim 5 is drawn to a protein "encoding for... a polynucleotide sequence comprising SEQ ID NO:1". Polynucleotides encode proteins; presumably, Applicant intended the claim to read "encoded by". The Examiner additionally notes that SEQ ID NO:1 is a rabbit sequence.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al., U.S. patent 6046157, filed 1995 in view of Jacobs et al., U.S. patent 5605690, 1997, or, alternatively, Nikawa et al. (Gene, 1994, vol. 149, pages 367-372), in view of Lin et al. and Jacobs et al.

These claims encompass the extracellular region of the splice variant of TGFβ RII taught by Nikawa et al. as a fusion protein with Fc, and, because "splice variant" is not so defined as to distinguish which of the two known forms of the receptor is the variant, also encompass the extracellular region of the TGFβ RII taught by Lin et al. expressed as a fusion protein. Lin et al., however, teaches methods using soluble TGFβ RII receptors to inhibit TGFβ function (see claims, columns 37-40). Lin et al. fails to teach Fc fusion proteins. However, such fusion proteins are taught by Jacobs et al. for soluble TNFα receptors (see figures1 and 3-6, columns 2, 7, 19, and 20, for example). Jacobs et al. fails to teach TGFβ RII fusion proteins. However, it

would have been obvious to one of ordinary skill in the art to combine the teachings of Lin et al. with those of Jacobs et al. to produce such a fusion protein. One of ordinary skill would have been motivated to do so because Lin et al. teaches the use of soluble TGFβ RII receptors to lower TGFβ levels, and Jacobs et al. teaches the use of such fusion proteins in an analogous system, soluble TNFα receptors, for use in lowering TNFα levels, and teaches that such fusion proteins are effective and may have particular advantages (column 7, lines 52-54). Neither Lin et al. or Jacobs et al. teach the splice variant of TGFβ RII taught by Nikawa et al. However, it would have been obvious to one of ordinary skill to construct a fusion protein of this variant as taught by Jacobs et al. for use to lower TGFβ levels as taught by Lin et al. One of ordinary skill would have been motivated to do so because Lin et al. teaches that type II receptors are useful for this purpose, and Nikawa et al. teaches the splice variant as a type II receptor.

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet Andres, Ph.D., whose telephone number is (703) 305-0557. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564. The fax phone number for this group is (703) 305-3014 or (703) 308-4242.

Communications via internet mail regarding this application, other than those under U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to **[yvonne.eyler@uspto.gov]**.

All Internet email communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark Office on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Janet Andres, Ph.D.
November 15, 2001

Yvonne Eyler

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